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REVIEW

Combinational Diuretics in Heart Failure

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Abstract

Purpose of Review Diuretics are the cornerstone therapy for acute heart failure (HF) and congestion. Patients chronically exposed to loop diuretics may develop diuretic resistance as a consequence of nephron remodelling, and the combination of diuretics will be necessary to improve diuretic response and achieve decongestion. This review integrates data from recent research and offers a practical approach to current pharmacologic therapies to manage congestion in HF with a focus on combinational therapy.

Recent Findings Until recently, combined diuretic treatment was based on observational studies and expert opinion. Recent evidence from clinical trials has shown that combined diuretic treatment can be started earlier without escalating the doses of loop diuretics with an adequate safety profile.

Summary Diuretic combination is a promising strategy for overcoming diuretic resistance in HF. Further studies aiming to get more insights into the pathophysiology of diuretic resistance and large clinical trials confirming the safety and efficacy over standard diuretics regimens are warranted.

Keywords Heart failure · Diuretics · Furosemide · Thiazides · Acetazolamide · Spironolactone

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Introduction

The heart failure (HF) syndrome was described as an emerging epidemic about 25 years ago [1]. Today, HF remains a serious clinical and public health problem as the total number of patients living with HF is increasing, reflecting the chronic course of the disease as well as population growth and ageing [1]. HF hospitalizations represent 1 to 2% of all hospital admissions, and HF is the most common diagnosis in hospitalized patients aged > 65 years. HF survival has improved substantially in the last decades but, unfortunately, remains prohibitively high [1].

Over the past decades, a multitude of new therapies for the management of patients with HF have shown benefit, especially for HF with reduced ejection fraction (HFrEF). The more recently updated clinical practice guidelines emphasize the importance of early and rapid initiation of guideline-directed medical therapies (GDMTs) that can improve life expectancy [2, 3].

More than 80% of patients with acute heart failure (AHF) present with signs and symptoms of congestion, which is the main reason why these patients seek medical care [4]. Given this pivotal role of congestion in AHF, diuretics are still a cornerstone of therapy in AHF [5].

In the early stages of HF, patients usually respond well to single-loop diuretic therapy. As the disease progresses, other comorbidities appear, such as renal failure, and patients are chronically exposed to loop diuretics, and consequently, the diuretic efficiency decreases [6]. In our clinical practice, up to 20–30% of patients with HF treated with loop diuretics will require admission for decompensation and a combination of diuretics to improve the diuretic response and achieve decongestion [6, 7].

The aim of this review is to integrate data from recent research and offer a practical approach to current pharmacologic therapies to manage congestion in HF, with a focus on combinational therapy.

The Rationale for Combining Diuretics: Diuretic Resistance and Pre-emptive Sequential Nephron Blockade

Poor response to diuretics is a crucial important clinical problem in patients with AHF, and the underlying pathophysiological mechanisms are diverse: impaired absorption, decreased renal blood flow, azotaemia, hypoalbuminemia, and proteinuria (resulting in reduced levels of active diuretics in the tubular lumen) might affect diuretic effectiveness [8, 9].

Furthermore, chronic diuretic treatment dramatically increases the capacity of the distal nephron to reabsorb delivered sodium chloride (NaCl), leading to the secondary decline in natriuresis (it is the so-called "braking phenomenon"). Secondary increases in NaCl absorptive capacity are associated with remarkable nephron remodelling, with hypertrophy of the distal convoluted tubule, connecting tubule, and collecting duct, which bypasses the proximal effect of the loop diuretic and results in enhanced sodium retention. These morphological and functional alterations, described almost four decades ago [10, 11], are the basis for the lack of diuretic efficacy in patients chronically treated with loop diuretics [8, 9, 12].

Similar to the classification of acute kidney injury, an anatomically based categorization of the mechanisms of diuretic resistance in HF has been proposed dichotomizing diuretic resistance in pre-renal and intrarenal. Pre-renal mechanisms appear to be proportionately less important in patients with HF where intrarenal mechanisms dominate. Intrarenal mechanisms are further divided based on the anatomic nephron segments in which the resistance mechanism arises (pre-loop of Henle, loop of Henle, and post-loop of Henle) (Fig. 1). Although most filtered sodium is reabsorbed in the proximal tubule and loop of Henle, most data from animal models and current human literature indicates that the post-loop of Henle tubular mechanisms (compensatory distal tubular sodium reabsorption) has the greater contribution to diuretic resistance in HF [8, 13]. In this sense, a recent mechanistic study investigated the two main mechanisms of diuretic resistance in HF (decreased tubular delivery of furosemide to its site of action and decreased tubular responsiveness) and compared chronic furosemide users vs. furosemide naïve patients [14•]. The greater diuretic response in loop diuretic naïve patients was not due to better loop diuretic delivery to the nephron, as both groups had similar estimated glomerular filtration rate (eGFR)-adjusted cumulative furosemide urinary excretion. Instead, the greater diuretic response in diuretic naïve patients was due to a better tubular response to furosemide [14•]. These findings indicate that diuretic resistance in chronic loop diuretic therapy is mainly driven by decreased tubular responsiveness rather than insufficient furosemide tubular delivery. Further studies aiming to better elucidate the pathophysiology of diuretic resistance would be necessary to personalize diuretic strategies by adapting them to nephron remodelling.

More recently, there has been an increase in the interest of sequential nephron blockade as a pre-emptive strategy in patients with AHF. In this scenario, sequential nephron blockade has been applied in patients who were not demonstrably diuretic resistant, but instead, it has been used as an approach to accelerating the relief of signs and symptoms of congestion.

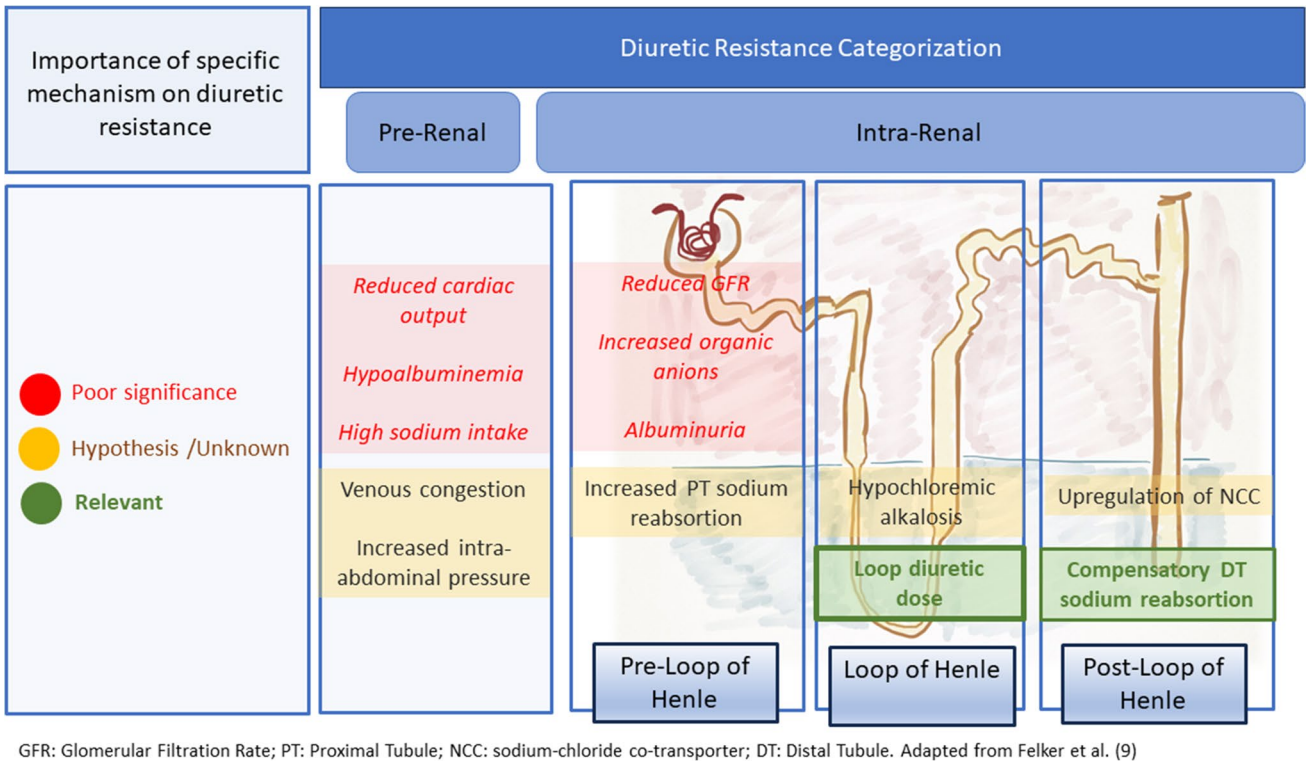

Fig. 1 Mechanisms of diuretic resistance

Combining Mineralocorticoid Receptor Antagonists with Loop Diuretics

Low-dose mineralocorticoid receptor antagonists (MRAs) as neurohormonal antagonists are a well-established treatment to improve survival in patients with HFrEF, but the role of high-dose MRAs in AHF remains uncertain. Some studies have shown that high-dose MRAs may result in significant natriuresis and clinical improvement. For instance, a single-centre, single-blind, nonrandomized study suggested that the benefits of high-dose MRA therapy in AHF included lower natriuretic peptide levels, less clinical congestion, better renal function, and less need for an intravenous diuretic [15]. However, the first large clinical trial on pre-emptive combined diuretic treatment (ATHENA-HF trial: Efficacy and Safety of Spironolactone in Acute Heart Failure) that randomized 360 patients with AHF treated with loop diuretics to receive high doses of spironolactone (100 mg per day) or placebo for 96 h did not improve the primary endpoint (change in N-terminal pro-B-type natriuretic peptide levels) or any of the secondary efficacy endpoints (clinical congestion score, dyspnoea assessment, net urine output, and net weight change) [16]. Despite the limitations of the ATHENA-HF trial, given its neutral results and the concerns regarding safety (hyperkalaemia and kidney dysfunction), the use of MRA at high doses is not recommended.

Combining Acetazolamide with Loop Diuretics

The mechanism of action of acetazolamide is primarily through the inhibition of carbonic anhydrase, which leads to increased excretion of bicarbonate, sodium, and water in the urine, producing a diuretic effect [17]. Recently, the ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload) trial, a multicentre, randomized, double-blind, placebo-controlled trial, included 519 patients with AHF with evidence of volume overload to receive pre-emptive or early acetazolamide (500 mg intravenously for 3 days) or placebo added to treatment with loop diuretics [18••]. All patients were receiving oral maintenance diuretic therapy with at least 40 mg of furosemide (or an equivalent dose of other loop diuretics). Concomitant treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i) and an estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m^2 were exclusion criteria. The trial intervention led to significantly greater rates of successful decongestion 3 days after randomization. In addition, the acetazolamide group achieved more natriuresis, shorter hospital stays, and more chances of getting discharged without residual congestion. The effect of acetazolamide on the primary endpoint was consistent across prespecified subgroups, except for patients receiving a higher maintenance dose of loop

diuretics, who had less benefit than those receiving a lower maintenance dose. Therefore, it is questionable whether acetazolamide will be useful as a diuretic resistance treatment strategy. In terms of safety, the incidence of worsening renal function (WRF) (defined as the doubling of the serum creatinine level from baseline, a decrease of at least 50% in the eGFR, or receipt of renal-replacement therapy), hypokalaemia, hypotension, and adverse events were similar in the two groups [18••]. However, when WRF was defined as an increase in creatinine of at least 0.3 mg/dL, acetazolamide was associated with a higher incidence of this event (40.5% vs. 18.9%) [19]. The prespecified subanalysis of the trial showed that the intervention was successful at achieving decongestion across the entire range of renal function (with more pronounced beneficial effects in patients with lower eGFR), and baseline left-ventricle ejection fraction (LVEF) [19, 20]. Furthermore, acetazolamide was effective over the entire range of baseline serum bicarbonate, but some signals indicated that patients with more elevated bicarbonate exhibited a more pronounced response to acetazolamide, and this fact could indicate that this form of diuretic resistance could be targeted by acetazolamide [21].

It is essential to mention that patients on SGLT2i (drugs with a mechanism of action also in the proximal tubule) were excluded, and then the generalizability of the results of the ADVOR trial among patients on SGLT2i remains unclear and will require further studies.

It is also important to consider that some measures taken by the investigators to mitigate adverse events, such as daily magnesium infusions and administering intravenous sodium bicarbonate or potassium when serum bicarbonate was below 20 mEq/L or when serum potassium was below 4 mEq/L, respectively, are not easy to replicate in clinical practice and should be considered necessary co-interventions when adding acetazolamide.

Combining Thiazide with Loop Diuretics

Thiazides inhibit the sodium-chloride cotransporter in distal convoluted tubules [22]. The evidence supporting a thiazide and loop diuretic combination in AHF has been limited to observational studies and a single 40-patient randomized study conducted before the current era of HF foundational therapy [23, 24]. All these previous studies suggest that combination diuretic therapy using any of several thiazide-type diuretics can significantly increase urine sodium excretion and induce weight loss and oedema resolution. However, there has always been concern about the potential adverse events of this diuretic strategy, such as severe hypokalaemia, hyponatremia, hypotension, and worsening renal function [23].

The CLOROTIC (Combining loop with thiazide diuretics for decompensated heart failure) trial was a pragmatic clinical trial that answered some of these questions. In this multicentre, randomized, double-blind, placebo-controlled trial, patients hospitalized due to AHF with at least 1-month prior treatment with an oral loop diuretic (furosemide dose 80–240 mg or equivalent) were assigned to receive oral hydrochlorothiazide (HCTZ) or placebo for 5 days, in addition to a standardized intravenous furosemide regimen. The use of high doses of furosemide at baseline is a surrogate indicator that many patients included in the CLOROTIC trial were resistant to loop diuretics. Oral HCTZ doses were adjusted according to three eGFR categories as follows: >50 mL/min/1.73 m^2, 25 mg once daily; 20–50 mL/min/1.73 m^2, 50 mg once daily; and <20 mL/min/1.73 m^2, 100 mg once daily [25••]. The main finding was that HCTZ resulted in greater weight loss at 72 h compared with placebo. The coprimary endpoint of patient-reported dyspnoea within the same time frame showed no significant differences between diuretic strategies. The effect of HCTZ on the primary endpoint was consistent across different subgroups. Safety outcomes were also assessed, including the proportion of patients whose serum creatinine increased by 0.3 mg/dL (>26.5 µmol/L), which occurred more commonly in patients receiving HCTZ vs. placebo (46% vs. 17%). Rates of severe hypokalaemia or hyponatraemia were also similar between diuretic strategies, as were the secondary endpoints of survival, HF rehospitalizations, and other serious adverse events. However, in a post hoc analysis using higher potassium cut-off points (≤ 3.5 and ≤ 3.0 mmol/L), hypokalaemia was more frequent in those who received HCTZ [25••].

Similarly to the ADVOR trial, post hoc subanalysis showed that the addition of eGFR-adjusted doses of oral HCTZ to loop diuretics in patients with AHF improved diuretic response across the eGFR spectrum, but this effect tended to be larger at higher eGFR [26]. Two additional post hoc subanalyses have shown that the trial intervention was consistent across the entire range of LVEF [27] and without differences according to sex [28].

Combining Sodium-Glucose Cotransporter-2 Inhibitors with Loop Diuretics

Two small clinical trials (EMPA-REPONSE-AHF and EMPAG-HF) analyzed for the first time the effect on decongestion of the pre-emptive initiation of a SGLT2i in patients with AHF. In both trials, the early addition of empagliflozin (10 mg and 25 mg in the EMPA-REPONSE-AHF and EMPAG-HF trials, respectively) to standard diuretic therapy increased the urine output without affecting renal function. However, there were no differences in the

dyspnoea scores and changes in body weight in comparison to placebo [29, 30].

The EMPULSE trial (empagliflozin in patients hospitalized for acute heart failure) showed that the pre-emptive or early initiation of empagliflozin vs. placebo in 530 patients hospitalized for AHF resulted in a significant clinical benefit in the 90 days after starting treatment [31]. A prespecified substudy of this trial evaluated the effect of empagliflozin on decongestion-related endpoints (weight loss, weight loss adjusted for diuretic dose, change from baseline in NT-proBNP, haemoconcentation and clinical congestion score). The initiation of empagliflozin in patients hospitalized for AHF resulted in an improvement in all the decongestion endpoints. This reduction was observed at all evaluated time points (15, 30, and 90 days) and, additionally, patients with greater weight loss (above the median) were more likely to experience a net clinical benefit at 90 days [32••].

The DICTATE-AHF trial examined the efficacy and safety of dapagliflozin initiated within 24 h of hospital presentation on diuretic response in patients with AHF. Although the primary outcome did not achieve significance, the results of this trial show a trend toward increased diuretic efficiency with the addition of dapagliflozin compared with placebo among patients admitted with AHF and requiring intravenous loop diuretics [33].

A small multicentre, open label, randomized clinical trial (DAPARESIST trial) compared the addition of dapagliflozin or metolazone to loop diuretic treatment in patients hospitalized with HF who remained congested despite treatment with intravenous furosemide, this being a surrogate marker of diuretic resistance [34]. The study suggests that both dapagliflozin and metolazone were similarly effective at relieving congestion when added to intravenous furosemide in patients with diuretic resistance. However, in our opinion, some of the results discussed in the DAPARESIST trial might be an overinterpretation and should be commented on in depth. First, in the DAPARESIST trial, the dose of metolazone was chosen at physicians' discretion (5 or 10 mg) based on their clinical experience and was not adjusted for renal function, resulting in a rather low median daily dose of 5.4 mg daily. Second, treatment groups at baseline were not balanced in terms of congestion. Patients assigned to receive metolazone had more signs of congestion: more elevated jugular venous pressure, pulmonary crepitations, ascites, and pleural effusion and higher scores in a modified ADVOR clinical congestion score than those assigned to dapagliflozin. Finally, the cumulative and median doses of loop diuretics after randomization were higher in patients who received dapagliflozin. As such, one might also conclude that patients assigned to dapagliflozin had lower diuretic efficiency than those assigned to (low dose) metolazone despite being less congested and receiving higher doses of furosemide. Now that most HF patients will be treated with an SGLT2i at baseline, we believe the main question is not whether these will be superior to diuretics in achieving decongestion but whether the sequential nephron blockade combining different classes of diuretics (loop diuretics plus thiazide diuretics and/or acetazolamide) on top of SGLT2i will be safe and provide incremental decongestion efficacy. Treatment with SGLT2i was not recommended for HF during the enrolment period of the CLOROTIC trial and was an exclusion criterion for the ADVOR trial. Data from the abovementioned trials support the early initiation of an SGLT2i in AHF to facilitate decongestion while rapidly and safely optimizing GDMT. Considering the benefits reported with SGLT2i in patients with HF in the acute setting [31, 34], the demand for safe and efficacious combination diuretic regimens may need re-evaluation in AHF cohorts with concomitant SGLT2i use.

Other Diuretic Combination Strategies

Tolvaptan, a competitive vasopressin V2-receptor antagonist, is an oral diuretic that acts on the distal portion of the nephron, promoting free water excretion. Evidence from clinical trials showed that tolvaptan, in combination with loop diuretics, is well tolerated in patients with congestive HF [35]. It also ameliorates symptoms of congestion, increases sodium concentration in patients with hyponatremia, reduces loop diuretic dose, and lowers the risk of hypokalaemia. However, these findings are inconsistent among studies, and moreover, these studies were not focused on patients with diuretic resistance [35, 36]. A possible scenario in which the usefulness of tolvaptan has been suggested is in patients with refractory HF and hyponatremia [37]. Based on these considerations, the DR-AHF (Tolvaptan add-on Therapy to Overcome Loop Diuretic Resistance in Acute Heart Failure With Renal Dysfunction) trial is an ongoing study designed to demonstrate the effectiveness of early tolvaptan as add-on therapy in AHF patients with renal dysfunction and diuretic resistance [38].

On the other hand, several studies (mostly conducted in European countries) have shown that administration of intravenous hypertonic saline (HS) given concomitantly with high doses of loop diuretics can improve diuresis, renal function, and clinical outcomes in patients with AHF [39]. However, the use of HS in AHF has been questioned by the scientific community for different reasons, including a retraction and subsequent exclusion from a meta-analysis based on concerns regarding data validity [40]. This retraction, in conjunction with the counterintuitive nature of administering salt in an effort to remove salt, is one of the reasons why HS has never been included in the guidelines [5] and has led to a slow adoption of this treatment strategy in many countries, including the United States [41]. These

Table 1 Comparison of combination diuretic trials in acute heart failure

	ATHENA-HF 22 sites (USA) *N* = 360	ADVOR 27 sites (Belgium) *N* = 519	CLOROTIC 26 sites (Spain) *N* = 230	DAPA-RESIST 7 sites (UK) *N* = 61	DICTATE-AHF *N* = 240	EMPULSE* 118 sites (15 countries) *N* = 530
Study design						
Intervention	High-dose spironolactone (100 mg) vs. placebo (or 25 mg spironolactone) for 4 days	IV acetazolamide (500 mg) vs. placebo for 3 days	Oral hydrochlorothiazide (eGFR > 50 mL/min: 25 mg; eGFR 20–50 mL/min: 50 mg; eGFR < 20 mL/min: 100 mg) vs. placebo for 5 days	Dapagliflozin 10 mg vs. Metolazone 5–10 mg for 3 days	Dapagliflozin 10 mg vs. placebo until day 5 or hospital discharge	Empagliflozin 10 mg vs. placebo for 90 days
Primary endpoint	Change in NT-proBNP levels from baseline to 96 h	Successful decongestion 3 days after randomization	Changes in weight and patient-reported dyspnoea at 72 h	Change in weight from randomization to 96 h	Diuretic efficiency (weight loss per 40 mg of furosemide) at day 5	Hierarchical composite of all-cause death, HF events, or a ≥ 5 point change in the KCCQ-TSS at 90 days
Secondary endpoints	1. Clinical congestion score 2. Changes in patient-reported dyspnoea 3. Diuresis at 96 h 4. Change in weight at 96 h 5. Loop diuretic dose at discharge 6. Development of in-hospital WHF 7. All-cause mortality and all-cause readmission at 30 days	1. Mortality or HF readmission at 90 days 2. Hospital length of stay	1. Changes in weight and patient-reported dyspnoea at 96 h 2. Metrics of diuretic response[a] 3. Hospital length of stay 4. Mortality and/or readmission at 30/90 days	1. Change in congestion assessed using LUS 2. Loop diuretic efficiency (weight loss per 40 mg of furosemide) 3. Modified ADVOR congestion score	1. Worsening AHF during index hospitalization 2. Readmission for AHF or diabetes mellitus 3. 24-h diuresis 4. 24-h natriuresis	1. Weight loss 2. Loop diuretic efficiency (weight loss per 40 mg of furosemide) 3. Change in NT-proBNP levels over 30 days of treatment 4. Hemoconcentration 5. Clinical congestion score
Safety endpoints	WRF: increase in serum creatinine > 0.3 mg/dL Hyperkalaemia (moderate > 5.5 mmol/L and severe > 6.0 mmol/L)	WRF: increase in serum creatinine × 2 or decrease in eGFR > 50% Hypokalaemia (K + < 3.0 mmol/L) Hypotension (SBP < 85 mmHg)	WRF: increase in serum creatinine > 0.3 mg/dL or decrease in eGFR > 50% Hypokalaemia (K + < 2.5 mmol/L)[b] Hiponatremia (Na + < 125 mmol/L)[b] Hypotension (SBP < 90 mmHg)	WRF: increase in serum creatinine > 0.3 mg/dL Hypokalaemia (K + < 3.5 mmol/L) Hiponatremia (Na + < 125 mmol/L) Hyperkalaemia (K + > 5.5 mmol/L)	1. Diabetic ketoacidosis 2. Hypotension 3. Hypoglycaemia 4. Genitourinary infections 5. Median change in eGFR	Acute renal failure (including acute kidney injury, subacute kidney injury, anuria, oliguria, azotaemia, renal failure, renal impairment, and renal replacement therapy)
Baseline characteristics						
Age (years)	65	78	83	79	65	71
Female sex	36%	37%	48%	54%	39%	34%
Hypertension	84%	75%	89%	N.A	N.A	80%

Table 1 (continued)

	ATHENA-HF 22 sites (USA) *N* = 360	ADVOR 27 sites (Belgium) *N* = 519	CLOROTIC 26 sites (Spain) *N* = 230	DAPA-RESIST 7 sites (UK) *N* = 61	DICTATE-AHF *N* = 240	EMPULSE* 118 sites (15 countries) *N* = 530
Diabetes mellitus	41%	47%	57%	46%	71%	45%
Atrial fibrillation	48%	72%	69%	67%	N.A	49%
Ischemic aetiology	63%	45%	33%	33%	N.A	25%
LVEF (%)	34%	43%	55%	45%	N.A	31%
Preserved LVEF (%)	27% (LVEF > 45%)	57% (LVEF > 40%)	75% (LVEF > 40%)	56% (LVEF > 40%)	48% (LVEF > 40%)	32% (LVEF > 40%)
Creatinine (mg/dL)	1.2	1.5	1.4	1.5	N.A	N.A
eGFR (mL/min/1.73m^2)[c]	56	39	43	41	53	52
NT-proBNP (pg/mL)	4102	6173	4525	4053		3202
Baseline treatment						
ACEi/ARB/ARNI	60%	52%	55%	31%	N.A	70%
Beta-blocker	74%	81%	60%	74%	N.A	79%
MRA	11%	42%	35%	36%	N.A	52%
Loop diuretics	96%	100%	100%	89%	N.A	82%
Dose of oral furosemide (mg/day)	80	60	80	N.A	N.A	N.A
Main findings	Adding high-dose spironolactone in AHF did not improve the primary or secondary efficacy end points. There were no safety concerns as high-dose spironolactone was safe and well tolerated	The addition of acetazolamide to loop diuretic therapy in patients with AHF resulted in a greater incidence of successful decongestion with no safety concerns	Adding oral hydrochlorothiazide to IV furosemide improved the diuretic response in patients with AHF but was associated with higher rates of WRF and hypokalaemia	Dapagliflozin was not more effective at relieving congestion than metolazone. Patients assigned to dapagliflozin received a larger cumulative dose of furosemide but experienced less biochemical upset	Early dapagliflozin initiation did not result in a statistically significant improvement in diuretic efficiency but did not worsen any prespecified safety outcomes	Initiation of empagliflozin in patients hospitalized for AHF resulted in an early, effective and sustained decongestion which was associated with clinical benefit at day 90

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *IV* intravenous, *KCCQ-TSS* Kansas City Cardiomyopathy Questionnaire Total Symptom Score, *LUS* lung ultrasound, *LVEF* left-ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *N.A.* not available, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *SBP* systolic blood pressure, *WHF* worsening heart failure, *WRF* worsening renal function

*Pre-specified subanalysis of decongestion-related endpoints of the EMPULSE study

[a]The metrics of diuretic response included a 24-h diuresis quantification, weight loss per 40 mg of furosemide (at 72 and at 96 h), net fluid loss (24-h diuresis) per milligramme of furosemide and mean loop diuretic dose administered from time of study enrollment to 72 h

[b]A post hoc analysis using higher K + (≤ 3.5 and ≤ 3.0 mmol/L) and Na + (< 130 mmol/L) cut-off points was also conducted

[c]An eGFR < 20 mL/min/1.73 m^2 was an exclusion criteria for the ADVOR, DAPA-RESIST, and EMPULSE trials; an eGFR < 25 mL/min/1.73 m^2 was an exclusion criteria for the DICTATE-AHF trial; an eGFR < 30 mL/min/1.73 m^2 was an exclusion criteria for the ATHENA-HF trial; in the CLOROTIC trial baseline, eGFR values were not an exclusion criterion, except if patients required renal replacement therapy

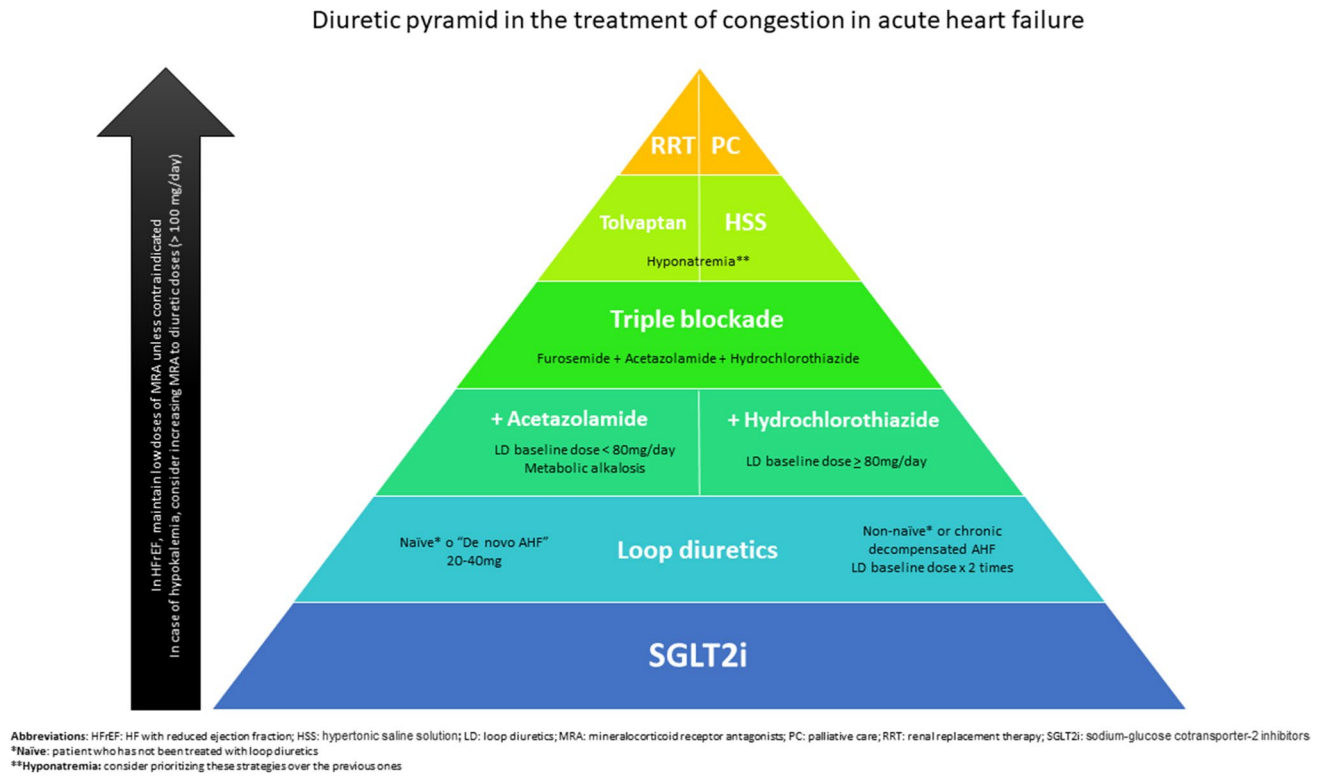
Diuretic pyramid in the treatment of congestion in acute heart failure
In HFrEF, maintain low doses of MRA unless contraindicated
In case of hypokalemia, consider increasing MRA to diuretic doses (> 100 mg/day)
RRT
PC
Tolvaptan
HSS
Hyponatremia**
Triple blockade
Furosemide + Acetazolamide + Hydrochlorothiazide
+ Acetazolamide
LD baseline dose < 80mg/day
Metabolic alkalosis
+ Hydrochlorothiazide
LD baseline dose ≥ 80mg/day
Naïve* o "De novo AHF"
20-40mg
Loop diuretics
Non-naïve* or chronic
decompensated AHF
LD baseline dose x 2 times
SGLT2i
Abbreviations: HFrEF: HF with reduced ejection fraction; HSS: hypertonic saline solution; LD: loop diuretics; MRA: mineralocorticoid receptor antagonists; PC: palliative care; RRT: renal replacement therapy; SGLT2i: sodium-glucose cotransporter-2 inhibitors
*Naïve: patient who has not been treated with loop diuretics
**Hyponatremia: consider prioritizing these strategies over the previous ones

Fig. 2 The diuretic pyramid

findings and arguments suggest that additional rigorous clinical trials, including HS as a therapeutic agent for AHF, are warranted [42].

Multinephron Segment Diuretic Therapy

Multinephron segment diuretic therapy (MSDT), defined as the simultaneous use of 3–4 diuretic classes with actions along the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct, is a potential method to overcome severe diuretic resistance in AHF. MSDT uses diuretics with action in multiple nephron segments to counter the nephron's adaptations. MSDT has been recommended for severe diuretic resistance with only expert opinion and case-level evidence, and its major barrier is the absence of safety data [43, 44]. A more recent retrospective study conducted in a United States centre included 167 patients hospitalized for AHF with diuretic resistance treated with simultaneous diuretics comprising an oral carbonic anhydrase inhibitor, intravenous loop diuretic, oral or intravenous thiazide, and oral MRA. MSDT was associated with a significant diuretic response in approximately two-thirds of the total cohort and one-half of patients with severe diuretic resistance without substantial changes in serum electrolytes, extreme electrolyte repletion, or worsening kidney function [45]. MSDT is an understudied but promising decongestive strategy in the AHF cohort with diuretic resistance but prospective and controlled studies are required.

Combinational Diuretics in the Ambulatory Setting

The few clinical trials on combined diuretic regimens have been carried out in hospital-admitted patients during the acute decompensation phase, with even less evidence during the post-discharge stable phase in the outpatient setting. Recently, the TRANSFORM-HF trial (the largest clinical trial of diuretics in outpatient HF patients) compared torsemide with furosemide in 2859 patients discharged after hospitalization for HF and did not find significant differences in all-cause mortality over 12 months. It would be interesting to know the effect of the concomitant use of thiazide diuretics with either torsemide or furosemide in this clinical trial, although this analysis was not reported [46]. A recent large multicentre observational cohort study conducted in Spain, including more than 14,000 patients discharged after an AHF hospitalization, found that 9.5% of patients were discharged with the combination of thiazide and loop diuretics, while the rest (90.5%) were discharged with only loop diuretics

on top of the rest of standard-of-care treatments. Combining thiazide and loop diuretics after discharge showed a neutral effect on all the analyzed outcomes (all-cause mortality and hospitalization) [47]. The DEA-HF (Heart Failure Diuresis Efficacy Comparison) study is an ongoing randomized, open-label, cross-over study comparing three diuretic regimens in patients with HF in the ambulatory setting (furosemide, furosemide plus metolazone, and furosemide plus acetazolamide) perhaps will provide some evidence in this context [48].

Practical Recommendations: the Diuretic Pyramid in the Treatment of Congestion in Acute Heart Failure

After reviewing the evidence from the latest clinical trials (summarized in Table 1) and based on our expertise, we propose a practical and personal approach to the combination of diuretics in patients with AHF (Fig. 2). Unless contraindicated, the vast majority of patients with AHF should be treated with a SGLT2i. The first therapeutic step should be loop diuretics, which should be prescribed depending on whether the patient is "de novo" or chronic decompensated HF and according to previous exposure to loop diuretics and congestion severity [5, 49]. In our opinion, the combination of diuretics is more justified in patients with chronic decompensated HF with prior exposure to high doses of loop diuretics and unequivocal data of congestion [22, 50]. We recommend an early addition of a second diuretic agent if diuretic resistance appears after loop diuretic optimization. The choice between HCTZ and acetazolamide can be controversial since there is no head-to-head comparison. HCTZ might be preferential in patients with diuretic resistance receiving chronic high doses of loop diuretics and acetazolamide in the case of metabolic alkalosis and/or lower chronic loop diuretic doses. In both cases, if baseline potassium is below 4 mEq/L, it is recommended to administer potassium chloride supplements. Although there is no evidence of triple blockade with the three drugs, this strategy could be the next therapeutic step if diuretic resistance persists. In case of hyponatremia, preference could be given to other treatment strategies for which there is less evidence, such as tolvaptan or HS with furosemide. In patients with HFrEF, we recommend maintaining low doses (25–50 mg/day) of MRA unless contraindicated, and in case of hypokalaemia, increasing the MRA to diuretic doses (> 100 mg/day) should be considered. In situations that are refractory to all of the above measures, the initiation of renal replacement therapy should be considered or, in the case of patients with advanced functional and/or cognitive impairment, consideration should be given to initiating symptomatic palliative treatment.

Conclusion

Until recently, the evidence on combined diuretic treatment in AHF was based on observational studies and expert experience. The recent evidence from clinical trials has shown that combined diuretic treatment can be started earlier without escalating the doses of loop diuretics with a good safety profile. However, more studies on the pathophysiology of diuretic resistance and larger clinical trials combining different diuretics would be necessary to personalize treatment by adapting it to nephron remodelling.

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Declarations

Competing Interests JC received consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis and Vifor Pharma (outside the submitted work). MCM reports personal fees or advisory boards from AstraZeneca, Boehringer Ingelheim, Bayer, Novartis, NovoNordisk, Rovi, and Vifor Pharma (outside the submitted work). JLMR received consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, Esteve and Zambon. JN reports personal fees or advisory boards from Alleviant, AstraZeneca, Boehringer Ingelheim, Bayer, Novartis, NovoNordisk, Pfizer, Rovi, and Vifor Pharma (outside the submitted work). LM reports personal fees or advisory boards from AstraZeneca, Boehringer Ingelheim, Lilly, Bayer, Novartis and Rovi (outside the submitted work). JCT and FF declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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